

**REMARKS**

Entry of the foregoing and reconsideration of the above-identified application in view of the foregoing amendments and the following remarks, are respectfully requested.

Applicants would first like to thank Examiner Brusca for the courtesy of granting the undersigned an interview to discuss this application. During the interview, Examiner Brusca indicated that claims appeared allowable upon submission of the signed Declaration of Dr. Horwitz. In addition, Applicants' representatives discussed with Examiner Brusca the declaration of an interference with various Kauffman claims, discussed in more detail below. The subject matter of new Claim 28 was likewise discussed, and Examiner Brusca indicated his intent to enter the present amendments.

Claim 28 finds support in the specification at least at page 2, lines 10-14, as well as at page 9, lines 6-8. No new matter is added by the present amendment.

Upon entry of new Claim 28, Claims 3, 4, 6-8 and 11-28 will be pending in this application. Claims 7, 8, 11, 12, 19, 20 and 27 are allowed, and Claims 3, 4, 6, 13-18 and 21-26 stand rejected under 35 U.S.C. §102(e) over Pieczenik.

The Examiner indicated that the outstanding rejection over Pieczenik would be withdrawn upon submission of the executed Declaration of Marshall Horwitz. Submitted herewith is the executed Declaration, and therefore, withdrawal of this rejection is respectfully requested.

The only remaining issue in this application is the declaration of an interference between Claims 3, 4, 6-8 and 11-28 of the instant Horwitz application and the following Kauffman claims:

Claims 1-48 of the Kauffman '323 Patent;  
Claims 1-5 of the Kauffman '192 Patent;  
Claims 1-53 of the Kauffman '483 Patent;  
Claims 1-46 of the Kauffman '514 Patent;  
Claims 1-107 of the Kauffman '476 Patent; and  
Claims 1-34 of the Kauffman '862 patent.

Applicants submitted a Request for Interference on June 9, 1999, and a Renewed Request for Interference on April 14, 2000. In response, the Examiner indicated the following:

[I]t is the Examiner's position that the Kauffmann applications do not disclose fully random peptide sequences, because the term stochastic used and claimed by Kauffmann was never defined in the Kauffmann applications as meaning random, and the examples of stochastic sequences disclosed in the Kauffmann applications do not result in fully random sequences.

While Applicants do not accept the Examiner's interpretation of the term "stochastic," in an effort to expedite the declaration of an interference, Applicants have amended the present claims such that the mixed population of nucleotide sequences "comprises" random sequences. Thus, the present invention is clearly directed to a method of identifying particular sequences among a mixture of what the Examiner would consider "fully" random and partially random sequences. Applicants note that the present specification describes as part of the claimed subject

matter, at least at page 9, lines 6-22 of the specification, randomized oligonucleotides which "may alternatively include first and second randomized regions (x and z nucleotides in length, respectively) that flank on either side a linker region (y nucleotides in length) of preselected sequence." Thus, such "randomized" oligonucleotides are indeed, not fully random (i.e., the oligonucleotide "comprises" randomized sequence). These specific oligonucleotides are claimed in new Claim 28.

According to 37 C.F.R. §1.601(n), "[i]nvention A is the same patentable invention as an invention 'B' when invention 'A' is the same as (35 U.S.C. §102) or is obvious (35 U.S.C. §103) in view of invention 'B' assuming invention 'B' is prior art with respect to invention 'A'" [emphasis in original].

Claims 1-48 of the Kauffman '323 Patent define the same patentable invention as claims 1-5 of the Kauffman '192 Patent and as claims 1-53 of the Kauffman '483 Patent and as claims 1-46 of the Kauffman '514 Patent and as claims 1-107 of the Kauffman '476 Patent and as claims 1-34 of the Kauffman '862 patent and as claims 3, 4, 6-8 and 11-28 of the instant Horwitz application, because they are all directed to methods utilizing populations of oligonucleotides, wherein the oligonucleotide "comprises" random sequences.

Moreover, the subject matter of the Kauffman claims, using the examiner's interpretation of the term "stochastic," is clearly the same invention as the subject matter of at least Claim 28 of the present application. Specifically, the Examiner has interpreted the term "stochastic" to reflect the results obtained in the Kauffman '323 patent at Column 5, lines 26-67.

---random DNA sequence---A<sub>(n)</sub>T<sub>(m)</sub>---random DNA sequence---  
---random DNA sequence---T<sub>(n)</sub>A<sub>(m)</sub>---random DNA sequence---

That the linker consisting of A's bound to T's which results from the above method of Kauffman does not lend patentability to the claimed method is confirmed in the Declaration of Phillip Patten, submitted herewith. Thus, the present claims are directed to the same invention as that of the above-noted Kauffman claims.

Therefore, Applicants respectfully request that an interference be declared employing the proposed Count set forth on attached Appendix B between claims 1-48 of the Kauffman '323 Patent, claims 1-5 of the Kauffman '192 Patent, claims 1-53 of the Kauffman '483 Patent, claims 1-46 of the Kauffman '514 Patent, claims 1-107 of the Kauffman '476 Patent, claims 1-34 of the Kauffman '862 patent and claims 3, 4, 6-8 and 11-28 of the instant Horwitz application, all

designated as corresponding to the Count. In addition, Applicants respectfully request that any pending Kauffman applications containing claims directed to the same patentable invention as defined in the Count be included in the interference.

Respectfully submitted,

Burns, Doane, Swecker & Mathis, L.L.P.

By: Sharon E. Crane  
R. Danny Huntington  
Registration No. 27,903  
Sharon E. Crane, Ph.D.  
Registration No. 36,113

P.O. Box 1404  
Alexandria, Virginia 22313-1404  
(703) 836-6620

Date: June 29, 2001

**Attachment to Amendment Pursuant to 37 C.F.R. § 116 filed June 29, 2001**

3. (Thrice Amended) A method of identifying a functional nucleotide sequence which provides a desired biological activity comprising:
- a. providing a means for detecting said desired biological activity;
  - b. synthesizing [a mixed population of random nucleotide sequences] by enzymatic or chemical synthesis a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said random sequences are [population is] synthesized without reference to a wild type sequence;
  - c. introducing a plurality of the [random] nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing the [random] nucleotide sequences;
  - d. introducing said cloning vectors into suitable host cells;
  - e. expressing said cloning vectors in said host cells; and
  - f. screening said host cells using said means for detecting the desired biological activity under conditions which allow detection of one or more host cells comprising vectors which comprise a functional nucleotide sequence which provides the desired biological activity.
4. (Thrice Amended) A method of isolating a functional nucleotide sequence which provides a desired biological activity comprising:
- a. providing a means for detecting said desired biological activity;

**Attachment to Amendment Pursuant to 37 C.F.R. § 116 filed June 29, 2001**

- b. synthesizing [a mixed population of random nucleotide sequences] by enzymatic or chemical synthesis a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said random sequences are [population is] synthesized without reference to a wild type sequence;
  - c. introducing a plurality of said [random] nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing the [random] nucleotide sequences;
  - d. introducing said cloning vectors into suitable host cells;
  - e. expressing said cloning vectors in said host cells;
  - f. screening said host cells using said means for detecting the desired biological activity under conditions which allow detection of one or more host cells comprising vectors which comprise a functional nucleotide sequence which provides the desired biological activity; and
  - g. isolating said nucleotide sequence or sequences which provide the desired biological activity.
6. (Thrice Amended) A method of isolating a host cell which comprises a functional nucleotide sequence which produces a desired biological activity comprising:
- a. providing a means for detecting said desired biological activity;

**Attachment to Amendment Pursuant to 37 C.F.R. § 116 filed June 29, 2001**

b. synthesizing [a mixed population of random oligonucleotides] by enzymatic or chemical synthesis a mixed population of oligonucleotides, wherein said oligonucleotides comprise random sequences, and wherein said random sequences are [population is] synthesized without reference to a wild type sequence;

c. introducing a plurality of said [random] oligonucleotides into a population of cloning vectors to obtain a plurality of cloning vectors containing the [random] oligonucleotides;

d. introducing said cloning vectors into suitable host cells;

e. expressing said cloning vectors in said host cells;

f. screening said host cells to determine whether the inserted oligonucleotide provides the desired biological activity;

g. isolating said host cells having said oligonucleotide having the desired biological activity.

7. (Thrice Amended) A method of producing a mixed population of random nucleotide sequences in order to identify one or more functional sequences which provide a desired biological activity comprising:

a. synthesizing a mixed population of [random] nucleotide sequences in a manner by which the frequency of stop codons in said mixed population is reduced as compared to codons encoding amino acids, wherein said nucleotide sequences comprise random sequences;  
and



**Attachment to Amendment Pursuant to 37 C.F.R. § 116 filed June 29, 2001**

b. inserting said mixed population of [random] nucleotide sequences into a population of cloning vectors to form a mixed population of vectors containing the nucleotide [randomly generated ] sequences.

8. (Twice Amended) An isolated, mixed population of vectors comprising [randomly generated] nucleotide sequences encoding a mixed population of amino acid sequences, wherein said nucleotide sequences comprise random sequences and [having] have a reduced frequency of stop codons as compared to codons encoding amino acids.

11. (Twice Amended) An isolated, mixed population of [random] nucleotide sequences, wherein said nucleotide sequences comprise random sequences [comprising a nucleotide sequence providing] and provide a desired biological activity produced by a method comprising synthesizing [a] the mixed population of [random] nucleotide sequences in a manner which biases against stop codons, and introducing a plurality of said [randomly generated] nucleotide sequences into a population of cloning vectors to form a mixed population of vectors containing [randomly generated] the nucleotide sequences.

12. (Thrice Amended) A method of identifying a functional nucleotide sequence which provides a desired biological activity comprising:

**Attachment to Amendment Pursuant to 37 C.F.R. § 116 filed June 29, 2001**

- a. providing a means for detecting said desired biological activity;
- b. synthesizing a mixed population of [random] nucleotide sequences in a manner by which the frequency of stop codons in said mixed population is reduced as compared to codons encoding amino acids, wherein said nucleotide sequences comprise random sequences;
- c. introducing a plurality of the [random] nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing the [random] nucleotide sequences;
- d. introducing said cloning vectors into suitable host cells;
- e. expressing said cloning vectors in said host cells; and
- f. screening said host cells using said means for detecting the desired biological activity under conditions which allow detection of one or more host cells comprising vectors which comprise a functional nucleotide sequence which provides the desired biological activity.

13. (Thrice Amended) A method of identifying a peptide, polypeptide or protein having a desired biological activity comprising:

- a. providing a means for detecting said desired biological activity;
- b. synthesizing [a mixed population of random nucleotide sequences] by enzymatic or chemical synthesis a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said random sequences are [population is] synthesized without reference to a wild type sequence;

**Attachment to Amendment Pursuant to 37 C.F.R. § 116 filed June 29, 2001**

c. introducing a plurality of said [random] nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing the [random] nucleotide sequences;

d. introducing said cloning vectors into suitable host cells;

e. expressing said cloning vectors in said host cells to produce a [random] population of peptides, polypeptides or proteins; and

f. screening said [random] population of peptides, polypeptides or proteins with said means for detecting the desired biological activity under conditions which allow detection of one or more peptides, polypeptides or proteins from said [random] population having the desired biological activity.

14. (Thrice Amended) A method of identifying a peptide, polypeptide or protein that reacts with a substrate:

a. providing a substrate;

b. synthesizing [a mixed population of random nucleotide sequences] by enzymatic or chemical synthesis a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said random sequences are [population is] synthesized without reference to a wild type sequence;

**Attachment to Amendment Pursuant to 37 C.F.R. § 116 filed June 29, 2001**

c. introducing a plurality of said [random] nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing the [random] nucleotide sequences;

d. introducing said cloning vectors into suitable host cells;

e. expressing said cloning vectors in said host cells to produce a [random] population of peptides, polypeptides or proteins; and

f. screening said [random] population of peptides, polypeptides or proteins with said substrate under conditions which allow detection of one or more peptides, polypeptides or proteins from said [random] population that react with said substrate.

15. (Twice Amended) A process for the production of a peptide or protein having a desired biological activity comprising the steps of:

producing by enzymatic or chemical synthesis a random population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said random sequences are [population is] produced without reference to a wild type sequence;

forming a library of expression vectors containing the [random] population of nucleotide sequences;

culturing host cells containing the vectors to produce peptides or proteins encoded by the [random] population of nucleotide sequences;

**Attachment to Amendment Pursuant to 37 C.F.R. § 116 filed June 29, 2001**

carrying out screening or selection on the host cells, to identify a peptide or protein produced by the host cells having the desired biological function;

isolating a [randomly] synthesized nucleotide sequence which encodes the identified peptide or protein; and

using the isolated sequence to produce the peptide or protein having the desired biological activity.

16. (Twice Amended) A method of identifying a peptide or protein having a desired biological activity, comprising:

(a) producing [a population of peptides or proteins encoded by random nucleotide sequences produced] by enzymatic or chemical synthesis a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said population of nucleotide sequences is produced without reference to a wild type sequence; and

(b) screening said population of peptides or proteins for said desired biological activity under conditions which allow detection of one or more peptides or proteins having said desired biological activity.

17. (Twice Amended) A method of producing a peptide or protein having a desired biological function, comprising:

**Attachment to Amendment Pursuant to 37 C.F.R. § 116 filed June 29, 2001**

- (a) producing [a population of peptides or proteins encoded by random nucleotide sequences produced] by enzymatic or chemical synthesis a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said population of nucleotide sequences is produced without reference to a wild type sequence;
- (b) screening said population of peptides or proteins for said desired biological function under conditions which allow detection of one or more peptides, polypeptides or proteins having said desired biological function;
- (c) isolating the nucleotide sequence(s) encoding said one or more peptides or proteins having said desired biological property; and
- (d) producing said peptide or protein.

18. (Twice Amended) A method of producing a [random polynucleotide population] mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said population is for use in screening for a desired biological function, comprising adding said nucleotide sequences [random nucleotides] to an expression vector without reference to a wild type sequence.

19. (Twice Amended) A method of generating a product of an enzyme-substrate reaction, comprising combining a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, [a population of peptides or proteins encoded

**Attachment to Amendment Pursuant to 37 C.F.R. § 116 filed June 29, 2001**

by random nucleotide sequences], wherein said population of nucleotide sequences is produced without reference to a wild type sequence, with substrate under conditions such that said enzyme-substrate reaction may occur, and incubating said population of peptides or proteins with said substrate such that said product may be detected.

20. (Twice Amended) A method of identifying a population of peptides or proteins which catalyze an enzyme substrate reaction, comprising:

(a) combining a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences [a population of peptides or proteins encoded by random nucleotide sequences], wherein said population of nucleotide sequences is produced without reference to a wild type sequence, with substrate under conditions such that said enzyme-substrate reaction may occur;

(b) incubating said population of peptides or proteins with said enzyme substrate so that a product of said enzyme-substrate reaction may be generated; and

(c) screening for the product of the enzyme-substrate reaction to identify a population of peptides or proteins which catalyze said enzyme-substrate reaction.

21. (Twice Amended) A process for the production of an expression vector capable of transcribing or translating an open reading frame to produce a desired biological function, said

**Attachment to Amendment Pursuant to 37 C.F.R. § 116 filed June 29, 2001**

vector comprising a [random] nucleotide sequence, wherein said nucleotide sequence comprises a random sequence, and wherein said process comprises [comprising] the steps of:

producing [a random population of nucleotide sequences] by enzymatic or chemical synthesis a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said population of nucleotide sequences is produced without reference to a wild type sequence;

ligating said mixed [random] population of nucleotide sequences into an expression vector to form a library of expression vectors;

transforming suitable host cells with said library of expression vectors;

growing the transformed host cells containing said expression vectors;

screening said transformed host cells in order to identify an expression vector capable of transcribing or translating an open reading frame to produce the desired biological function, or selecting said host cells containing an expression vector capable of transcribing or translating an open reading frame to produce the desired biological function;

isolating the identified or selected transformed host cell; and

isolating the expression vector from said isolated host cell.

22. (Twice Amended) A method for producing a heterogenous [random] population of vectors comprising:



**Attachment to Amendment Pursuant to 37 C.F.R. § 116 filed June 29, 2001**

(a) synthesizing a heterogenous mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said mixed population of nucleotide sequences comprises [population of random nucleotide sequences comprising] about a billion or more different nucleotide sequences, said method consisting of random ligation of oligonucleotides or random addition of nucleotide triphosphates without reference to a wild type sequence, and

(b) inserting said heterogenous mixed population of [random] nucleotide sequences into a population of vectors to form a heterogenous population of vectors [containing random nucleotide sequences].

23. (Twice Amended) A process for the production of a nucleotide sequence comprising,

producing [a heterogenous population of random nucleotide sequences] by enzymatic or chemical synthesis a heterogenous mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said population [of] is produced without reference to a wild type sequence;

inserting said population of [random] nucleotide sequences into vectors to form a [random] population of vectors;

introducing said [random] population of vectors into host cells in a manner to produce a [random] population of transformed host cells;

**Attachment to Amendment Pursuant to 37 C.F.R. § 116 filed June 29, 2001**

growing independent colonies from the transformed host cells;  
screening and/or selecting said colonies of the host cells to identify host cells comprising  
a nucleotide sequence having a desired biological activity; and  
isolating said nucleotide sequence from the selected or screened host cells.

24. (Twice Amended) A method of identifying a nucleotide sequence having a  
desired biological activity, comprising:

(a) producing [a population of nucleotide sequences comprising about a billion or more  
different random nucleotide sequences] by enzymatic or chemical synthesis a mixed population  
of about a billion or more different nucleotide sequences, wherein said nucleotide sequences  
comprise random sequences, and wherein said population is produced without reference to a wild  
type sequence;

(b) screening said population of nucleotide sequences for said desired biological activity  
under conditions which allow detection of nucleotide sequences having said desired biological  
activity.

25. (Twice Amended) A method of identifying a functional nucleotide sequence  
which provides a desired biological activity comprising:

a. providing a means for detecting said desired biological activity;

**Attachment to Amendment Pursuant to 37 C.F.R. § 116 filed June 29, 2001**

b. producing by enzymatic or chemical synthesis a heterogenous mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said population is produced without reference to a wild type sequence;

c. inserting said population of nucleotide sequences into vectors to form a population of vectors;

[b. forming a population of cloning vectors, each containing a random nucleotide sequence produced by enzymatic or chemical synthesis wherein said random nucleotide sequences are produced without reference to a wild type sequence;

c.] d. introducing said cloning vectors into suitable host cells;

e. [d.] expressing said cloning vectors in said host cells; and

f. [e.] screening said host cells using said means for detecting the desired biological activity under conditions which allow detection of one or more host cells comprising vectors which comprise a functional nucleotide sequence which provides the desired biological activity.

26. (Amended) A method of producing a host cell which provides a desired biological activity [comprising an expression vector, wherein said expression vector comprises at least one random nucleotide sequence] comprising:



**Attachment to Amendment Pursuant to 37 C.F.R. § 116 filed June 29, 2001**

a. producing by enzymatic or chemical synthesis a heterogenous mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said population is produced without reference to a wild type sequence;

b. inserting said population of nucleotide sequences into vectors to form a population of vectors;

[a. synthesizing a mixed population of random nucleotide sequences by enzymatic or chemical synthesis without reference to a wild type sequence;


b. inserting said mixed population of random nucleotide sequences into a population of cloning vectors to form a mixed population of vectors containing randomly generated sequences;] and

c. transforming a competent host cell with one of said vectors [a vector containing a randomly generated sequence].

27. (Amended) A method of producing a host cell which provides a desired biological activity [comprising an expression vector, wherein said expression vector comprises at least one random nucleotide sequence] comprising:

a. synthesizing [a mixed population of random single-stranded nucleotide sequences] using terminal transferase a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein the frequency of stop codons is reduced in comparison to codons encoding amino acids;

**Attachment to Amendment Pursuant to 37 C.F.R. § 116 filed June 29, 2001**

- 
- b. making said single-stranded sequences double-stranded using DNA polymerase;
  - c. producing a mixed population of vectors containing said nucleotide [randomly generated] sequences; and
  - d. transforming a competent host cell with one of said vectors [a vector containing a randomly generated sequence].